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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Glen R. Nemerow

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/903,327	<b>Applicant(s)</b> NEMEROW ET AL.	
	<b>Examiner</b> Anne Marie S. Wehbe	<b>Art Unit</b> 1632	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 November 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2-16, 18-27, 30, 32-34, 36, 37 and 40-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-16, 18-27, 30, 32-34, 36, 37 and 40-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \*   c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

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### **DETAILED ACTION**

Applicant's amendment and response received on 11/4/03 has been entered. As requested, claims 1, 17, 29, 31, 38, and 39 have been canceled, and new claims 40-45 have been added. Claims 2-16, 18-27, 30, 32-34, 36-37, and 40-45 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

#### ***Claim Rejections - 35 USC § 112***

The rejection of claims 6 and 13-14 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn over claim 6 and maintained in part over claims 13-14. Applicant's argument have been fully considered but have not been found persuasive in overcoming the rejection of record over claims 13-14.

The applicant has amended claims 13-14 to remove the lack of antecedent basis for "the nucleic acid encoding the antibody". However, the claims as amended are still confusing and indefinite it is unclear whether the applicant intend to recite a product by process claim, wherein the antibody portion of the bifunctional molecule is produced from the recited nucleic acid sequences. Claim 32, the base claim from which claims 13 and 14 depend, clearly recites a particle comprising a fiberless adenovirus particle, a bifunctional molecule comprising an

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antibody and a targeting agent, and an adenovirus genome. Claims 10 and 11, which depend on claim 32, now recite wherein the antibody comprises the sequence of amino acids set forth in SEQ ID NOS 2, 4, or 6. Amended claim 13, which depends on claim 10, now recites wherein the antibody portion is encoded by a sequence of nucleic acids selected from a group which includes SEQ ID NOS 1 or 5, sequences degenerate to SEQ ID NOS 1 or 5, or sequences that hybridize under high stringency to SEQ ID NOS 1 or 5. Claim 14, which depends on claim 11, has been amended in a similar fashion based on the nucleic acid sequence of SEQ ID NO:3. Since it is clear from the base claim that the particle comprises an antibody protein, the limitations in claims 13 and 14 regarding nucleic acid sequences is confusing since it is unclear whether the applicant is trying to claim the antibody made by a particular process or whether the applicant is actually reciting that the particle also comprises the nucleic acid sequence. Applicant's statement that the antibody portions are encoded by nucleic acids does not clarify this issue. Thus, the rejection of record stands.

Applicant's claim amendments have resulted in the following new grounds of rejection under 35 U.S.C. 112, second paragraph.

Claims 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 33 lacks antecedent basis for the term “the viral particle surface protein”. Claim 32, from which claim 33 depends, recites that the antibody “binds to an antigen in a protein on the particle”.

Claim 37 lacks antecedent basis for the term “delivery vector particle”. Claims 32, from which claim 37 depends has been amended such that it recites a fiberless adenoviral particle and not a “delivery vector” or “delivery vector particle”.

Claim 40 is indefinite in its recitation of “ a bifunctional molecule of claim 10”. Claim 10 has been amended to recite , “The targeted delivery particle of claim 32”, instead of a “bifunctional molecule”. Thus, the metes and bounds of the claim are unclear.

#### ***Claim Rejections - 35 USC § 102***

The rejection of claims 1-9, 12, 15-27, 29-34, and 36-37 under 35 U.S.C. 102(b) as being anticipated by WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al., is withdrawn in view of applicant’s amendments to the claims and arguments. However, please note that applicant’s amendments have necessitated new grounds of rejection of the claims under 35 U.S.C. 103(a) below.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 10-11, and 13-14 under 35 U.S.C. 103(a) as being unpatentable over WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al., in view of Stewart et al. (1997) EMBO J., Vol. 16, No. 6, 1189-1198, is withdrawn in view of applicant's amendments to the claims. However, please note the claim amendments have resulted in new grounds of rejection of the claims under 35 U.S.C. 103(a) below.

Claims 2-16, 18-27, 30, 32-34, 36-37, and 40-45 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/40508 (9/17/98), hereafter referred to as Sosnowski et al. in view of Von Seggern et al. (1999) J. Virol., Vol. 73(2), 1601-1608, Wickham et al. (1996) J. Virol., Vol. 70(10), 6831-6836, and Stewart et al. (1997) EMBO J., Vol. 16, No. 6, 1189-1198. Applicant's arguments as they apply to the instant grounds of rejection have been fully

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considered but have not been found persuasive in overcoming the rejection of record presented in detail below.

The applicant claims as amended recite targeted delivery vector particles comprising a fiberless adenovirus particle, a fiberless adenoviral genome, and a bifunctional molecule comprising an antibody that binds to a protein on the particle that binds to  $\alpha_v$  integrin and a targeting agent that binds to a cell surface protein that activates the phosphatidylinositol 3 signaling pathway. The applicant further claims said targeted delivery vector particle wherein the bifunctional molecule comprises all or a portion of the DAV-1 antibody, or wherein the antibody binding protein binds to the penton base of an adenovirus capsid protein or to a protein which includes an RGD motif, or wherein the targeting agent is an FGF or EGF or an agent which binds to the EGF or FGF receptors. In addition the applicant claims said particles wherein the antibody is a Fab'2 or Fab fragment, wherein the bifunctional molecule comprises a fusion protein or chemically conjugated polypeptides, or wherein the bifunctional molecule further comprises a peptide linker that links the antibody to the targeting agent. The applicant also claims a combination of the bifunctional molecule and a fiberless adenovirus vector which encodes a therapeutic protein. The applicant further claims said bifunctional molecule wherein the antibody binding protein binds to the penton base of an adenovirus capsid protein and wherein the amino acid sequence of the antibody comprises the amino acid sequence set forth in SEQ ID NOS. 2, 4, or 6 or a sufficient portion thereof for antigen recognition.

In regards to claims 13-14, the applicant claims said targeted delivery particles wherein the bifunctional molecule comprises an antibody portion comprises the amino acid sequence set forth in SEQ ID NOS. 2, 4, or 6 or a sufficient portion thereof for antigen

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recognition, and wherein the antibody is encoded by a nucleic acid selected from the coding portions of SEQ ID NOS 1, 3, or 5, sequences degenerate to SEQ ID NOS 1, 3, or 5 or sequences which hybridize under high stringency conditions to SEQ ID NOS 1, 3, or 5. As noted above in the rejection of claims 13-14 under 35 U.S.C. 112, second paragraph, the claims are confusing in that it is unclear whether the applicant is claiming the bifunctional antibody which is a protein or the nucleic acid sequences which encode the antibody portion of the bifunctional molecule. As noted above, subject matter drawn to nucleic acids has been non-elected in this application.

Further it is unclear whether applicant intended to claim a product by process where the antibody is produced from the recited nucleic acid sequences. For the purposes of examining the claims in regards to prior art, the claims have been interpreted as being drawn to the bifunctional molecule which is an antibody conjugated to a targeting agent. Since the product is an antibody with a particular amino acid sequence, the exact sequence of a nucleic acid which may encode the recited amino acid sequences does not carry patentable weight as the product, for the purposes of patentability, is defined by its structure and properties and not on the process or reagents used to make the product. Case law states that “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Sosnowski et al. teaches retargeted, tropism modified viral vector particles, particularly adenoviral vector particles which comprise an adenoviral genome encoding a



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therapeutic gene and which are complexed with a molecule that comprises a antibody which binds to a component of the viral capsid and a targeting antibody or protein which binds to receptors which are capable of internalization on target cells (Sosnowski et al., pages 4-5, and 171-174, claims 1-30). Sosnowski et al. further teaches that the viral capsid comprises penton base and penton fiber, and that the antibody can be targeted to the penton base (Sosnowski et al., pages 23-24, and page 26, lines 5-7). Sosnowski et al. also teaches examples of targeting proteins including FGF2, EGF, PDGF, VEGF and cytokines, and particularly suggest using FGF as the targeting protein (Sosnowski et al., pages 35-36). In more detail, Sosnowski et al. teaches that the antibody can be conjugated to the targeting ligand, or alternatively that the antibody and targeting ligand are a fusion protein (Sosnowski et al., page 6, lines 23-27). Sosnowski et al. also teaches that the conjugate of antibody and ligand can include a peptide linker, and that the conjugate can be produced by chemical coupling methods or by recombinant expression of chimeric DNA molecules (Sosnowski et al., page 16, lines 26-30). In addition, Sosnowski et al. teaches that the antibody can be a Fab fragment or a single chain antibody (Sosnowski et al., pages 29-30). In particular, Sosnowski et al. teaches that the tropism modified viruses can target and be internalized by cells which express the binding partner of the targeting ligand (Sosnowski et al., see for example pages 107-108). Finally, Sosnowski et al. teaches that in one embodiment of the invention, the native tropism of the viral particle is completely ablated and replaced with an entirely new tropism by either genetic, immunologic, or chemical means (Sosnowski et al., page 22, lines 18-22, pages 22-23, bridging paragraph, pages 26-27, and page 34).

Sosnowski et al. differs from the instant invention by not specifically teaching that the adenoviral vector particle is a fiberless adenoviral particle. However, as noted above, Sosnowski

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et al. does in fact teach using modified viruses would natural tropism has been completely ablated. Von Seggern et al. supplements Sosnowski et al. by teaching that a fiberless adenovirus particle which comprises a fiberless adenoviral genome loses its natural tropism for infecting epithelial cells (Von Seggern et al., page 1603-1604). Von Seggern et al. further teaches that the fiberless virus should be useful for vector re-targeting (Von Seggern et al., page 1601-1602, bridging sentence). Thus, based on the motivation for making modified adenoviral particles whose native tropism has been ablated and which have a new tropism derived from a targeting fusion protein comprising an antibody that binds to a viral capsid protein and FGF provided by Sosnowski et al., and the motivation provided by Von Seggern et al. for using a fiberless adenoviral particle in vector re-targeting, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the fiberless adenoviral vectors and particles taught by Von Seggern et al. in the methods of re-targeting viral particles using anti-capsid antibody/FGF targeting molecules taught by Sosnowski et al. Further, in view of the high level of skill in molecular and viral biology at the time of filing, the detailed instructions provided by Von Seggern et al. for making a fiberless adenoviral particle, and the detailed instructions provided by Sosnowski et al. for re-targeting adenoviral particles using an antibody that binds to the viral capsid combined with a targeting protein such as FGF, the skilled would have had a reasonable expectation of success in making a re-targeted adenoviral particle comprising a fiberless adenoviral particle and fiberless adenoviral genome and a bifunctional targeting molecule which comprises an antibody that targets a component of the viral capsid and a cell surface targeting protein such as FGF.

Sosnowski et al. further differ from the instant invention in that Sosnowski et al. does not teach a specific antibody which binds to the penton base of the capsid, or the DAV-1 antibody in particular. However, Sosnowski et al. does reference a prior art publication by Wickham et al. and suggests that the protein and particles described therein may be useful in the methods disclosed by Sosnowski et al. (Sosnowski et al., page 26, lines 5-7). Wickham et al. teaches modifying adenoviral tropism by complexing the adenoviral particle with a bispecific antibody that binds to a modified penton base on the viral particle and to integrin on surface of target cells (Wickham et al., page 6831). Thus, by specifically referencing Wickham et al., Sosnowski et al. provides specific motivation for modifying viral tropism by using a fusion protein comprising an antibody that binds to the penton base. Therefore, based on specific motivation to look to the teachings of Wickham et al. provided by Sosnowski et al., it would be *prima facie* obvious to the skilled artisan at the time of filing to make and use a targeting molecule as taught by Sosnowski et al. which comprises an antibody that targets the penton base, as taught by Wickham et al., and a cell surface targeting protein such as FGF with a reasonable expectation of success.

Regarding the DAV-1 antibody in particular, please note that the specification discloses that the DAV-1 antibody comprises the heavy and light chain amino acid sequences set forth in SEQ ID NOS: 2 and 4 and that SEQ ID NO: 6 is a portion of the heavy chain. Stewart et al. supplements Sosnowski et al. and Wickham et al. by teaching a DAV-1 antibody which binds to the penton base of adenovirus, specifically to the RGD containing motif IRGDTFATR (Stewart et al., pages 1189, and 1196). While Stewart et al. does not specifically disclose the amino acid sequences of the heavy and light chains of the full length DAV-1 antibody or the Fab

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fragment, the particular amino acid sequence of the DAV-1 antibody is intrinsic to the antibody itself, as the antibody is a protein which consists of amino acids. The skilled artisan would have motivated to substitute the DAV-1 antibody for the Wickham et al. antibody in the methods of re-targeting adenoviral particles taught by Sosnowski et al. in view of Von Seggern et al. based on the fact that the DAV-1 antibody recognizes the native penton base and thus the re-targeting method would not require modification of the penton base gene in the adenoviral genome. Thus, in order to simplify the re-targeting of the adenoviral particle, it would have been *prima facie* obvious to the skilled artisan to substitute the use the DAV-1 antibody over the anti-penton base antibody taught by Wickham et al. which recognizes a modified penton base protein in the methods of making a re-targeted adenoviral particle taught by Sosnowski et al. in view of Von Seggern. Further, based on the high level of skill in the art of molecule and viral biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in making a fiberless adenoviral particle complexed with a bifunctional molecule comprising the Fab fragment of DAV-1 and a targeting ligand such as FGF-2 capable of binding adenovirus and retargeting the virus to cells expressing the FGF receptor.

The applicant has provided arguments based on the previous rejection of record which was based on the teachings of Sosnowski et al. and Stewart et al. These arguments are moot in view of the new grounds of rejection which are based on the teachings of Sosnowski et al. in view of Von Seggern et al., Wickham et al., and Stewart et al. However, the applicant's particular concerns regarding the teachings of Sosnowski et al. and Stewart et al. as they apply to the new grounds of rejection have been addressed. Regarding Sosnowski et al., the applicant argues that Sosnowski et al. does not teach all of the claim limitations of the claims as amended,

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including fiberless adenoviral particles or genomes, and antibodies which bind to the penton base. In particular, the applicant argues that Sosnowski et al. only teaches antibodies to the fiber knob and does not teach or suggest antibodies against other components of the capsid. In response, the instant rejection points out that Sosnowski et al. clearly teaches ablating the natural tropism of the viral particles to improve retargeting and Von Seggern et al. has been cited to supplement Sosnowski et al. by teaching fiberless adenoviral particles and genomes which ablate the natural tropism of the adenovirus. Regarding antibodies to the penton base, the instant rejection points out that Sosnowski et al. broadly teaches using antibodies which recognize components of the capsid which include the penton base, and further specifically references a publication by Wickham et al. for teaching a targeting embodiment which is based on antibody recognition of the penton base. Wickham et al. has also been specifically cited in the instant rejection for teaching that a bispecific antibody can be used to bind the penton base and modify the tropism of the resulting viral particle. Thus, applicant's concerns regarding deficiencies in the teachings of Sosnowski et al. are moot in view of the teachings of Von Seggern et al. and Wickham et al.

Regarding the teachings of Stewart et al., the applicant argues that there is no motivation provided by either Sosnowski et al. or Stewart et al. to substitute the DAV-1 antibody for the antibodies taught by Sosnowski et al. In particular, the applicant argues that Stewart et al. does not teach bifunctional molecules, and further teaches that DAV-1 inhibits viral internalization. In response, motivation to utilize antibodies against the penton base are provided by the teachings of Sosnowski et al. to use antibodies against capsid components and by the specific reference to Wickham et al., which clearly teaches a bispecific targeting molecule that

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includes an antibody that binds to modified penton base. Further, the fact that Stewart et al. teaches that DAV-1 inhibits penton base mediated internalization does not teach away from its use in a bifunctional targeting molecule. Sosnowski et al. clearly teaches that in order to enhance targeting, it is important to ablate the natural tropism of the virus. Thus, the inhibition of penton base interaction with its receptor is actually a desired outcome, since the purpose of the methods of Sosnowski et al. are to re-direct the tropism of the viral particle such that the virus binds and is internalized through the FGF2 receptor. Therefore, applicant's concerns regarding Stewart et al. are not persuasive in view of the teachings of Sosnowski et al. and Wickham et al. and in view of the nature of the re-targeted viral particles taught by Sosnowski et al. Therefore, applicant's arguments regarding Stewart et al. have not been found compelling.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

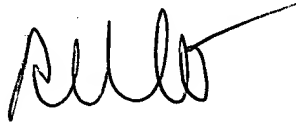
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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

**ANNE M. WEHBE PH.D**  
**PRIMARY EXAMINER**

A handwritten signature in black ink, appearing to read 'Anne M. Wehbé', with a long horizontal stroke extending to the right.